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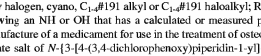
(54) **Title:** PIPERIDINE DERIVATIVES USEFUL FOR TREATING OSTEOARTHRITIS AND OSTEOARTROSIS



(57) **Abstract:** Use of a compound of formula (I): [Chemical formula should be inserted here. Please see paper copy] wherein: R^1 is phenyl optionally substituted by halogen, cyano, C_{1-6}#191 alkyl or C_{1-6}#191 haloalkyl; R^2 is hydrogen, C_{1-6}#191 alkyl or C_{1-6}#191 cycloalkyl; and R^3 is a group having an NH or OH that has a calculated or measured pKa of 1.0 to 8.0; or a pharmaceutically acceptable salt thereof; in the manufacture of a medicament for use in the treatment of osteoarthritis or osteoarthrosis. The invention also concerns the benzenesulfonate salt of *N*-{3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2,3-dihydro-2-oxo-4-(trifluoromethyl)-5-thiazolecarboxamide, a process for making it, and its use in therapy (for example in treating CCR3 mediated disease states).

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Piperidine derivatives useful for treating osteoarthritis and osteoartrosis

The present invention concerns piperidine derivatives having pharmaceutical activity as modulators of chemokine receptor (for example CCR3) activity and H1 antagonist activity in the treatment of osteoarthritis or osteoarthrosis. The invention also concerns a particular salt of a specific piperidine derivative.

Histamine is a basic amine, 2-(4-imidazolyl)-ethylamine, and is formed from histidine by histidine decarboxylase. It is found in most tissues of the body, but is present in high concentrations in the lung, skin and in the gastrointestinal tract. At the cellular level inflammatory cells such as mast cells and basophils store large amounts of histamine. It is recognised that the degranulation of mast cells and basophils and the subsequent release of histamine is a fundamental mechanism responsible for the clinical manifestation of an allergic process. Histamine produces its actions by an effect on specific histamine G-protein coupled receptors, which are of four main types, H1, H2 H3 and H4. Histamine H1 antagonists comprise the largest class of medications used in the treatment of patients with allergic disorders, for example rhinitis and urticaria. Antagonists of H1 are useful in controlling the allergic response by for example blocking the action of histamine on post-capillary venule smooth muscle, resulting in decreased vascular permeability, exudation and oedema. The antagonists also produce blockade of the actions of histamine on the H1 receptors on c-type nociceptive nerve fibres, resulting in decreased itching and sneezing.

Chemokines are chemotactic cytokines that are released by a wide variety of cells to attract macrophages, T cells, eosinophils, basophils and neutrophils to sites of inflammation and also play a role in the maturation of cells of the immune system. Chemokines play an important role in immune and inflammatory responses in various diseases and disorders, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. These small secreted molecules are a growing superfamily of 8-14 kDa proteins characterised by a conserved four cysteine motif. The chemokine superfamily can be divided into two main groups exhibiting characteristic structural motifs, the Cys-X-Cys (C-X-C, or α) and Cys-Cys (C-C, or β) families. These are distinguished on the basis of a single amino acid insertion between the NH-proximal pair of cysteine residues and sequence similarity.

The C-X-C chemokines include several potent chemoattractants and activators of neutrophils such as interleukin-8 (IL-8) and neutrophil-activating peptide 2 (NAP-2).

The C-C chemokines include potent chemoattractants of monocytes and lymphocytes, but not neutrophils, such as human monocyte chemotactic proteins 1-3 (MCP-1, MCP-2 and MCP-3), RANTES (Regulated on Activation, Normal T Expressed and Secreted), eotaxins and the macrophage inflammatory proteins 1 α and 1 β (MIP-1α and MIP-1β).

Studies have demonstrated that the actions of the chemokines are mediated by subfamilies of G protein-coupled receptors, among which are the receptors designated CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CXCR1, CXCR2, CXCR3 and CXCR4.

Pharmaceutically active N-(2-hydroxyprop-1-yl) piperidine derivatives having chemokine receptor modulatory activity and H1 antagonist activity are disclosed in WO2005/073192.

Osteoarthritis (OA) is a group of chronic, painful, disabling conditions affecting synovial joints and is characterized by the degeneration of matrix components of articular cartilage accompanied by the production of proinflammatory cytokines (Pelletier et al., *Rheum Dis Clin North Am* **19** (1993), pp. 545–568). Interleukin-1 (IL-1) beta is widely accepted as one of the proinflammatory cytokines that plays a role in the pathophysiology of OA (Dinarello, Interleukin-1, *Ann N Y Acad Sci* **546** (1988), pp. 122–132). The catabolic events occurring in chondrocytes include the up-regulation in genes of matrix metalloproteinases (MMPs), inducible nitric oxide synthase (iNOS) (Stadler *et al.*, *J Immunol* **147** (1991), pp. 3915–3920), cyclooxygenase-2 (COX-2) (Morisset et al., *J Rheumatol* **25** (1998), pp. 1146–1153) and microsomal prostaglandin E synthase-1 (mPGEs1) and the release of nitric oxide (NO) and prostaglandin E_2 (PGE_2)(Stichtenoth *et al.*, *J Immunol* **167** (2001), pp. 469–474). A concommitant retardation in the anabolic activities of the chondrocytes leads to a decline in proteoglycan and collagen synthesis (Benton and Tyler, *Biochem Biophys Res Commun* **154** (1988), pp. 421–428, and *Coll Relat Res* **8** (1988), pp. 393–405).

Recent studies have shown that a number of G-Protein coupled receptors (GPCRs) and their ligands exhibit altered expression patterns in OA cartilage or in primary

chondrocytes isolated from this tissue (Alaaeddine et al 2001, Arthritis Rheum. 2001, 44(7) 1633-1642, Tetlow and Woolley, *Inflamm. Res* **54, suppl 1** (2005) S74-S75).

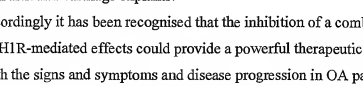
The present invention is based on the finding that both the H1R and the chemokine CCR3 receptors are expressed at elevated levels in OA cartilage and their ligands are present at high levels in OA synovial fluid.

It has been found that histamine via the H1R regulates expression of PGE2, IL-6 and IL-8 in primary chondrocytes. Histamine dose-dependently induces PGE2 release from primary cultures of human chondrocyte and has been found to elevate COX-2 mRNA, and histamine and IL-1 act synergistically to regulate PGE2 expression in primary chondrocytes and in OA explant cartilage. The prevailing dogma has classified OA as a non-inflammatory joint disease. However, more recently clinical studies have demonstrated a high correlation between radiographic OA and inflammation (D'Agostino et al, *Ann Rheum Dis* **64** (2005), pp1703-1709) and have linked inflammatory changes and synovitis with progression of structural changes in OA (Ayral et al, *Osteoarthritis Cart* **13** (2005), pp361-367). Thus, histamine driven increases in expression of inflammatory mediators IL6, IL8 and PGE2 may play a pivotal role in OA disease progression. In addition to its role as a key mediator of inflammation, PGE2 is implicated in osteoarthritic pain via its well documented role as a sensitiser of peripheral nociceptor terminals and histamine stimulation of articular primary sensory afferents may also contribute to the mechanical hyperalgesia observed in OA.

The present inventors have also found that the CCR3 ligand, Eotaxin-2, increases expression of a number of cartilage degrading matrix metalloproteases and ADAMTS4 from human articular cartilage explants.

Accordingly it has been recognised that the inhibition of a combination of both CCR3 and H1R-mediated effects could provide a powerful therapeutic approach for treating both the signs and symptoms and disease progression in OA patients.

Accordingly, the present invention provides the use of a compound of formula (I):



(I)

wherein:

R^1 is phenyl optionally substituted by halogen, cyano, C_{1-4} alkyl or C_{1-4} haloalkyl;

R^2 is hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl; and

R^3 is a group having an NH or OH that has a calculated or measured pKa of 1.0 to 8.0;

or a pharmaceutically acceptable salt thereof;

in the manufacture of a medicament for use in the treatment of osteoarthritis or osteoarthrosis.

It will be appreciated that treatment refers to both therapy or prophylaxis, unless otherwise indicated.

Compounds of formula (I) are disclosed in WO2005/073192 (published 11 August 2005). pKa's of compounds of formula (I) are calculated or measured according to the methodologies described in WO2005/073192.

Certain compounds of formula (I) can exist in different isomeric forms (such as enantiomers, diastereomers, geometric isomers or tautomers). The present invention covers the use of all such isomers and mixtures thereof in all proportions.

Suitable salts include acid addition salts such as a hydrochloride, dihydrochloride, hydrobromide, phosphate, sulfate, acetate, diacetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulfonate or *p*-toluenesulfonate. Further examples of acid addition salts are: bisulphate, benzenesulphonate (besylate), pyruvate, succinate, ethanesulphonate, malonate, xinafoate, ascorbate, oleate, nicotinate, saccharinate, adipate, formate, glycolate, L-lactate, D-lactate, aspartate, malate, L-tartrate, D-tartrate, stearate, 2-furoate, 3-furoate, napadisylate (naphthalene-1,5-disulfonate or naphthalene-1-(sulfonic acid)-5-sulfonate), edisylate (ethane-1,2-disulfonate or ethane-1-(sulfonic acid)-2-sulfonate), isethionate (2-hydroxyethylsulfonate), 2-mesitylenesulphonate and 2-naphthalenesulphonate. Salts also include metal salts, such as an alkali metal salt (for example a sodium or potassium salt) or an alkaline earth metal salt (for example magnesium or calcium).

The compounds of formula (I) may exist as solvates (such as hydrates) and the present invention covers the use of all such solvates.

Halogen is, for example fluorine or chlorine.

Alkyl groups and moieties are straight or branched chain and are, for example, methyl, ethyl, n-propyl, iso-propyl or tert-butyl.

Cycloalkyl is monocyclic and is, for example, cyclopropyl, cyclopentyl or cyclohexyl.

Haloalkyl is an alkyl group carrying one or more (such as 1 to 6) halogen (such as chloro or fluoro atoms) and is, for example, CF_3, CH_2CF_3 or C_2F_5.

Fluoroalkyl is an alkyl group carrying one or more (such as 1 to 6) fluoro atoms and is, for example, CH_2F, CF_3, CH_2CF_3 or C_2F_5.

In one aspect the present invention provides the use of a compound of formula (I) wherein R^1 is phenyl optionally substituted by halogen, cyano or C_{1-4} alkyl.

In another aspect the present invention the use provides a compound of formula (I) wherein R^1 is phenyl substituted with one, two or three of: halogen (such as fluoro or chloro), cyano or C_{1-4} alkyl (such as methyl); for example R^1 is phenyl substituted by one, two or three of: fluoro, chloro, methyl or cyano. In another aspect R^1 is phenyl substituted by one, two or three (such as two or three) of: fluoro, chloro, cyano or methyl (such as chloro, cyano or methyl). R^1 is, for example, 3,4-dichlorophenyl, 2-methyl-3-chloro-4-cyanophenyl, 2-methyl-4-chlorophenyl, 3-methyl-2,4-dichlorophenyl, 2-methyl-3,4-dichlorophenyl, 3-chloro-4-cyanophenyl, 3,4-difluorophenyl, 3-fluoro-4-chlorophenyl or 4-chlorophenyl (such as 2-methyl-4-chlorophenyl, 3-methyl-2,4-dichlorophenyl, 2-methyl-3,4-dichlorophenyl, 3-chloro-4-cyanophenyl, 3,4-difluorophenyl, 3-fluoro-4-chlorophenyl or 4-chlorophenyl). In a still further aspect R^1 is 3,4-dichlorophenyl or 3-chloro-4-cyanophenyl.

In a further aspect of the invention R^1 is phenyl substituted by one or more of chloro or methyl and optionally further substituted by fluoro. For example R^1 is 2-methyl-4-chlorophenyl, 3-methyl-2,4-dichlorophenyl, 2-methyl-3,4-dichlorophenyl, 3-fluoro-4-chlorophenyl, 4-chlorophenyl or 3,4-dichlorophenyl.

In another aspect of the invention R^1 is 3,4-dichlorophenyl, 2-methyl-4-chlorophenyl, 3-methyl-2,4-dichlorophenyl, 2-methyl-3,4-dichlorophenyl or 2-methyl-3-chloro-4-cyanophenyl.

In a still further aspect the present invention provides the use of a compound of formula (I) wherein R^2 is hydrogen or C_{1-4} alkyl (such as methyl).

In yet another aspect of the invention R^2 is hydrogen.

The acidic NH (that is the NH having a calculated or measured pKa of 1.0 to 8.0) of R^3 can be part of a ring or it can be part of a substituent on an aryl or heterocyclyl ring. The acidic OH (that is the OH having a calculated or measured pKa of 1.0 to 8.0) of R^3 can be a substituent or part of a substituent (such an OH in a carboxylic acid group) on an aryl

or heterocyclyl ring. Thus, for example, the acidic OH of R^3 can be part of an acidic phenol, in a carboxylic acid, or in a hydroxy aromatic heterocyclyl (such as a hydroxypyridine which may tautomerise to a pyridone).

Aryl includes optionally substituted phenyl and naphthyl.

Heterocyclyl is an optionally substituted aromatic or non-aromatic 5- or 6-membered ring, comprising, as required, at least one heteroatom selected from the group comprising nitrogen, oxygen and sulphur; or an N-oxide thereof, or an S-oxide or S-dioxide thereof. Heterocyclyl is, for example, furyl, thienyl (also known as thiophenyl), pyrrolyl, 2,5-dihydropyrrolyl, thiazolyl (for example in 2-oxo-2,3 -dihydro- 1,3 -thiazolyl), isothiazolyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, triazolyl (for example in 1*H*-1,2,3 -triazolyl), pyridinyl (for example in 6-oxo- 1 ,6-dihydro-pyridinyl) or pyrimidinyl.

In an aspect of the present invention the acidic NH of R^3 is part of a suitably substituted ring (for example part of a pyrrolyl, 2,5-dihydropyrrolyl, thiazolyl, isothiazolyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, triazolyl, pyridinyl or pyrimidinyl ring) or part of a substituent on a suitably substituted aryl (for example phenyl or naphthyl) or suitably substituted heterocyclyl (for example furyl, thienyl, pyrrolyl, 2,5-dihydropyrrolyl, thiazolyl, isothiazolyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, triazolyl, pyridinyl or pyrimidinyl) ring.

In another aspect of the present invention the acidic OH of R^3 is a substituent or part of a substituent (such an OH in a carboxylic acid group) on a suitably substituted aryl (for example phenyl or naphthyl) or suitably substituted heterocyclyl (for example furyl, thienyl, pyrrolyl, 2,5-dihydropyrrolyl, thiazolyl, isothiazolyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, triazolyl, pyridinyl or pyrimidinyl) ring. Thus, for example, the acidic OH of R^3 can be part of an acidic phenol (substituted or unsubstituited), in a carboxylic acid, or in a suitably substituted hydroxy aromatic heterocyclyl (such as a hydroxypyridine which may tautomerise to a pyridone). Further examples of suitably substituted hydroxy aromatic hcterocyclyl are hydroxyquinolines, hydroxyisoquinolines and hydroxybenzimidazoles.

In one aspect of the present invention when the acidic NH of R^3 is part of a suitably substituted ring it is, for example, part of a 2-oxo-thiazol-5-yl, 2-oxo-oxazol-5-yl, 2-oxo-imidazol-5-yl, 1H-1 ,2,3-triazol-4-yl, 4-oxo-1H-1,4-dihydropyridin-3-yl, 2,6-dioxo-1H-

1,2,3,6-tetrahydropyrimidin-4-yl, 6-oxo-1H-1,6-dihydropyridin-3 -yl or 2H-tetrazol-5-yl ring.

In another aspect of the present invention when the acidic NH of R^3 is part of a suitably substituted ring it is, for example, part of a 2-oxo-thiazol-5-yl, 1H-1,2,3-triazol-4-yl or 6-oxo-1H-1,6-dihydropyridin-3-yl ring.

In a further aspect of the present invention when the acidic NH of R^3 is part of a substituent it is, for example, part of $NHS(O)_2(C_{1-4}$ alkyl).

In another aspect the present invention provides the use of a compound of formula (I) wherein R^3 is a group having an NH or OH that has a calculated or measured pKa of 3 to 6.5.

In yet another aspect the present invention provides the use of a compound of formula (I) wherein R^3 is a group having an NH or OH that has a calculated or measured pKa of 1.0 to 8.0 (for example 3 to 6.5), the group R^3 being, for example,

- 2-oxo-thiazol-5-yl having a suitable electron withdrawing substituent {such as C_{1-4} fluoroalkyl (for example CF_3, CH_2CF_3 or C_2F_5), an aryl group (for example 4-fluorophenyl), a heterocyclyl group (for example pyridyl) or a group $CH_2S(O)_2(C_{1-4}$ alkyl)} in the 4-position;
- 2-oxo-oxazol-5-yl having a suitable electron withdrawing substituent {such as C_{1-4} fluoroalkyl (for example CF_3, CH_2CF_3 or C_2F_5) or $CH_2S(O)_2(C_{1-4}$ alkyl)} in the 4-position;
- 1H-1,2,3-triazol-4-yl having a suitable substituent {such as C_{1-4} alkyl (for example CH_3 or $CH(CH_3)_2$), C_{3-6} cycloalkyl (for example cyclopropyl), C_{1-4} fluoroalkyl (for example CF_3, CH_2CF_3 or C_2F_5), S-R^4 (wherein R^4 is C_{1-4} alkyl [for example CH_3], C_{1-4} fluoroalkyl [for example CF_3, CH_2CF_3 or C_2F_5] or C_{3-6} cycloalkyl [for example cyclopropyl]), $NHS(O)_2(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl$)S(O)_2(C_{1-4}$ alkyl), an aryl group (for example 4-fluorophenyl), a heterocyclyl group (for example pyridyl) or a group $CH_2S(O)_2(C_{1-4}$ alkyl)} in the 5-position;
- 4-oxo-1H-1,4-dihydropyridin-3-yl having a suitable electron withdrawing substituent {such as C_{1-4} fluoroalkyl (for example CF_3 or C_2F_5)} in the 2-position;
- 2,6-dioxo-1H-1,2,3,6-tetrahydropyrimidin-4-yl having a suitable substituent {such as C_{1-4} alkyl (for example CH_3), C_{3-6} cycloalkyl (for example cyclopropyl) or $CH_2(C_{1-3}$ fluoroalkyl) (for example CH_2CF_3)} in the 3-position and optionally

substituted in one or more other ring positions;

- 6-oxo-1H-1,6-dihydropyridin-3 -yl having a suitable electron withdrawing substituent {such as C_{1-4} fluoroalkyl (for example CF_3, CH_2CF_3 or C_2F_5), cyano or phenyl} in the 2-position and/or the 5-position and optionally substituted in one or more other ring positions;
- 6-oxo-1H-1,6-dihydropyridin-3-yl having CH_2CO_2H on the ring nitrogen and optionally substituted in one or more other ring positions;
- 2H-tetrazol-5-yl;
- a CO_2H, CH_2CO_2H or OCH_2CO_2H group on an optionally substituted phenyl, optionally substituted CH_2phenyl, optionally substituted naphthyl ring or optionally substituted acylated (such as with $C(O)(C_{1-4}$ alkyl)) dihydroisoquinolinyl ring; or,
- an $NHS(O)_2(C_{1-4}$ alkyl) (for example $NHS(O)_2CH_3$) group on an optionally substituted aromatic heterocyclyl ring (for example pyridinyl, pyrimidinyl or thiazolyl);

or, where possible, a tautomer thereof.

In one aspect of the invention acylated (such as with $C(O)(C_{1-4}$ alkyl)) dihydroisoquinolinyl carries the CO_2H, CH_2CO_2H or OCH_2CO_2H group on position 7.

In yet another aspect the present invention provides the use of a compound of formula (I) wherein R^3 is a group having an NH or OH that has a calculated or measured pKa of 1.0 to 8.0 (for example 3 to 6.5), the group R^3 being, for example,

- 2-oxo-thiazol-5-yl having a suitable electron withdrawing substituent {such as C_{1-4} fluoroalkyl (for example CF_3, CH_2CF_3 or C_2F_5), an aryl group (for example 4-fluorophenyl), a heterocyclyl group (for example pyridyl) or a group $CH_2S(O)_2(C_{1-4}$ alkyl)} in the 4-position;
- 2-oxo-oxazol-5-yl having a suitable electron withdrawing substituent {such as C_{1-4} fluoroalkyl (for example CF_3, CH_2CF_3 or C_2F_5) or $CH_2S(O)_2(C_{1-4}$ alkyl)} in the 4-position;
- 1H-1,2,3-triazol-4-yl having a suitable substituent {such as C_{1-4} alkyl (for example CH_3), C_{3-6} cycloalkyl (for example cyclopropyl), C_{1-4} fluoroalkyl (for example CF_3, CH_2CF_3 or C_2F_5), S-R^4 (wherein R^4 is C_{1-4} alkyl [for example CH_3], C_{1-4} fluoroalkyl [for example CF_3, CH_2CF_3 or C_2F_5] or C_{3-6} cycloalkyl [for example cyclopropyl]),

$NHS(O)_2(C_{1-4}$ alkyl), an aryl group (for example 4-fluorophenyl), a heterocyclyl group (for example pyridyl) or a group $CH_2S(O)_2(C_{1-4}$ alkyl)} in the 5-position;

- 4-oxo-1H-1,4-dihydropyridin-3-yl having a suitable electron withdrawing substituent {such as C_{1-4} fluoroalkyl (for example CF_3 of C_2F_5)} in the 2-position;
- 2,6-dioxo-1H-1,2,3,6-tetrahydropyrimidin-4-yl having a suitable substituent {such as C_{1-4} alkyl (for example CH_3), C_{3-6} cycloalkyl (for example cyclopropyl) or $CH_2(C_{1-3}$ fluoroalkyl) (for example CH_2CF_3)} in the 3-position;
- 6-oxo-1H-1,6-dihydropyridin-3-yl having a suitable electron withdrawing substituent {such as C_{1-4} fluoroalkyl (for example CF_3, CH_2CF_3 or C_2F_5) or cyano} in the 2-position or the 5-position and optionally substituted in other positions;
- 2H-tetrazol-5-yl;
- a CO_2H group on an optionally substituted phenyl or naphthyl ring; or,
- an $NHS(O)_2(C_{1-4}$ alkyl) (for example $NHS(O)_2CH_3$) group on an optionally substituted aromatic heterocyclyl ring (for example pyridinyl, pyrimidinyl or thiazolyl);

or, where possible, a tautomer thereof.

Where indicated above that a heterocyclyl ring in R^3 may be optionally substituted it can be optionally substituted by, for example: fluoro, chloro, bromo, C_{1-4} alkyl (for example methyl), C_{3-6} cycloalkyl (for example cyclopropyl), C_{1-4} fluoroalkyl (for example CF_3, CH_2CF_3 or C_2F_5), S-R^4 (wherein R^4 is C_{1-4} alkyl [for example CH_3], C_{1-4} fluoroalkyl [for example CF_3, CH_2CF_3 or C_2F_5] or C_{3-6} cycloalkyl [for example cyclopropyl]), cyano, $S(O)_2(C_{1-4}$ alkyl) (for example $S(O)_2CH_3$) or $S(O)_2NH(C_{1-4}$ alkyl) (for example $S(O)_2NHCH_3$).

Where indicated above that a phenyl or naphthyl ring in R^3 may be optionally substituted it can be optionally substituted by, for example, halogen, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} fluoroalkyl (for example CF_3, CH_2CF_3 or C_2F_5)}, OCF_3, SCF_3, nitro, $S(C_{1-4}$ alkyl), $S(O)(C_{1-4}$ alkyl), $S(O)_2(C_{1-4}$ alkyl), $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$, $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl).

In one aspect of the invention R^3 is:

- 2-oxo-thiazol-5-yl having C_{1-4} fluoroalkyl (for example CF_3, CH_2CF_3 or C_2F_5) in the 4-position;
- 1H-1,2,3-triazol-4-yl having a suitable substituent {such as C_{1-4} alkyl (for example

CH_3) or S-R^4 (wherein R^4 is C_{1-4} fluoroalkyl [for example CF_3, CH_2CF_3 or C_2F_5])} in the 5-position;

- 2,6-dioxo- 1*H*-1,2,3,6-tetrahydropyrimidin-4-yl having a suitable substituent {such as C_{1-4} alkyl (for example CH_3) or C_{1-4} fluoroalkyl (for example CF_3, CH_2CF_3 or C_2F_5)} in the 3-position;
- 6-oxo-1H-1,6-dihydropyridin-3-yl having a suitable electron withdrawing substituent {such as C_{1-4} fluoroalkyl (for example CF_3, CH_2CF_3 or C_2F_5) or cyano} in the 2-position or the 5-position and optionally substituted in other positions;
- a CO_2H group on an optionally substituted naphthyl ring; or,
- an $NHS(O)_2(C_{1-4}$ alkyl) (for example $NHS(O)_2CH_3$) group on an optionally substituted aromatic heterocyclyl ring (for example pyridinyl, pyrimidinyl or thiazolyl);

or, where possible, a tautomer thereof; the optional substituents being as defined above.

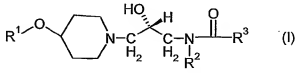
In yet another aspect the present invention provides the use of a compound of formula (I) wherein R^3 is:

- 2-oxo-thiazol-5-yl having a suitable electron withdrawing substituent {such as C_{1-4} fluoroalkyl (for example CF_3, CH_2CF_3 or C_2F_5), a phenyl group (for example 4-fluorophenyl) or a heterocyclyl group (for example pyridyl)} in the 4-position;
- 1H-1,2,3-triazol-4-yl having a suitable substituent {such as C_{1-4} alkyl (for example CH_3 or $CH(CH_3)_2$), C_{1-4} fluoroalkyl (for example CF_3, CH_2CF_3 or C_2F_5), S-R^4 (wherein R^4 is C_{1-4} alkyl [for example CH_3] or C_{1-4} fluoroalkyl [for example CF_3, CH_2CF_3 or C_2F_5]), $N(C_{1-4}$ alkyl)$S(O)_2(C_{1-4}$ alkyl) or a phenyl group (for example 4-fluorophenyl)} in the 5-position; or,
- 6-oxo-1H-1,6-dihydropyridin-3-yl having C_{1-4} fluoroalkyl (for example CF_3, CH_2CF_3 or C_2F_5) or cyano in the 2-position or the 5-position.

In another aspect the present invention provides a compound of formula (I) wherein R^3 is:

- 2-oxo-thiazol-5-yl having CF_3 or C_2F_5 in the 4-position;
- 1H-1,2,3-triazol-4-yl having CF_3, C_2F_5, SCF_3, SCH_2CF_3 or SC_2F_5 (for example CF_3 or SCH_2CF_3) in the 5-position; or,
- 6-oxo-1H-1,6-dihydropyridin-3-yl having CF_3 or C_2F_5 in the 2-position.

In yet another aspect the present invention provides the use of a compound of formula (I) wherein the 2-hydroxy group has the stereochemistry shown below:



(I)

In a further aspect the present invention provides the benzenesulfonate salt of *N*-{3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2,3-dihydro-2-oxo-4-(trifluoromethyl)-5-thiazolecarboxamide (which is an example of pharmaceutically acceptable salt form of a compound of formula (I)). In a still further aspect the present invention provides the benzenesulfonate salt of *N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2,3-dihydro-2-oxo-4-(trifluoromethyl)-5-thiazolecarboxamide.

In a still further aspect the present nvention provides a process for the preparation of the benzenesulfonate salt of *N*-{3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2,3-dihydro-2-oxo-4-(trifluoromethyl)-5-thiazolecarboxamide comprising treating *N*-{3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2,3-dihydro-2-oxo-4-(trifluoromethyl)-5-thiazolecarboxamide with benzenesulfonic acid in a suitable solvent (such as an aliphatic alcohol, for example methanol) at ambient temperature (for example 0-35°C).

Compounds of formula (I) can be prepared by methods described, or analogous to those described, in WO 2005/073192. Intermediates for such processes can be prepared by methods described, or analogous to those described in WO 2005/073192.

In a further aspect the invention provides a compound for use according to the invention, the compound being:

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-6-oxo-2-(trifluoromethyl)-1,6-dihydropyridine-3-carboxamide;

N-{(2*R*)-3-[4-(2,4-Dichloro-3-methylphenoxy)piperidin-1-yl]-2-hydroxypropyl}-6-oxo-2-(trifluoromethyl)-1,6-dihydropyridine-3-carboxamide;

5-Bromo-*N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-6-oxo-2-(trifluoromethyl)-1,6-dihydropyridine-3-carboxamide;

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2,3-dihydro-2-oxo-4-(trifluoromethyl)-5-thiazolecarboxamide;

N-{(2*S*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-*N*-methyl-2-oxo-4-(trifluoromethyl)-2,3-dihydro-1,3-thiazole-5-carboxamide;

N-{(2*S*)-3-[4-(2,4-Dichloro-3-methylphenoxy)piperidin-1-yl]-2-hydroxypropyl}-N-methyl-2-oxo-4-(trifluoromethyl)-2,3-dihydro-1,3-thiazole-5-carboxamide;

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-oxo-4-(pentafluoroethyl)-2,3-dihydro-1,3-thiazole-5-carboxamide;

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-5-methyl-1H-1,2,3-triazole-4-carboxamide;

N-{(2*R*)-3-[4-(2,4-Dichloro-3-methylphenoxy)piperidin-1-yl]-2-hydroxypropyl}-5-methyl-1H-1,2,3-triazole-4-carboxamide;

5-Cyano-*N*-{(2*R*)-3-[4-(3 ,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-6-oxo-2-(trifluoromethyl)-1,6-dihydropyridine-3–carboxamide;

5-Cyano-*N*-{(2*R*)-3-[4-(2,4-dichloro-3-methylphenoxy)piperidin-1-yl]-2-hydroxypropyl}-6-oxo-2-(trifluoromethyl)-1,6-dihydropyridine-3–carboxamide;

5-Cyano-*N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-6-oxo-2-phenyl-1,6-dihydropyridine-3–carboxamide;

5-Cyano-*N*-{(2*R*)-3-[4-(2,4-dichloro-3-methylphenoxy)piperidin-1-yl]-2-hydroxypropyl}-6-oxo-2-phenyl-1,6-dihydropyridine-3–carboxamide;

5-Cyano-*N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-6-oxo-2-(trifluoromethyl)-1,6-dihydropyridine-3–carboxamide;

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2,6-dioxo-3-(2,2,2-trifluoroethyl)-1,2,3,6-tetrahydropyrimidine-4-carboxamide;

5-Cyano-2-cyclopropyl-*N*-[(2*R*)-3-[4-(3,4-dichlorophenoxy)-1-piperidinyl]-2-hydroxypropyl]-1,6-dihydro-6-oxo-3–pyridinecarboxamide;

5-Cyano-2-cyclopropyl-N-[(2*R*)-3-[4-(2,4-dichloro-3-methylphenoxy)-1-piperidinyl]-2-hydroxypropyl]-1,6-dihydro-6-oxo-3–pyridinecarboxamide;

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-6-[(methylsulfonyl)amino]-4-(trifluoromethyl)nicotinamide;

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-5-[(2,2,2-trifluoroethyl)thio]-1*H*-1,2,3-triazole-4-carboxamide;

4-[({(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}amino)-carbonyl]-1-naphthoic acid;

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-[(methylsulfonyl)amino]-4-(trifluoromethyl)-1,3-thiazole-5-carboxamide;

N-{(2*R*)-3-[4-(4-Chloro-2-methylphenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-oxo-4-(trifluoromethyl)-2,3-dihydro-1,3-thiazole-5-carboxamide;

[5-[({(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}amino)-carbonyl]-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl]acetic acid;

N-{(2*R*)-3-[4-(3,4-Dichloro-2-methylphenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-oxo-4-(trifluoromethyl)-2,3-dihydro-1,3-thiazole-5-carboxamide;

N-{(2R)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-4-(4-fluorophenyl)-2-oxo-2,3-dihydro-1,3-thiazole-5-carboxamide;

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-5-(4-fluorophenyl)-1*H*-1,2,3-triazole-4-carboxamide;

N-{(2*R*)-3-[4-(3-Chloro-4-cyanophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-oxo-4-(trifluoromethyl)-2,3-dihydro-1,3-thiazole-5-carboxamide;

N-{(2*S*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-oxo-4-(trifluoromethyl)-2,3-dihydro-1,3-thiazole-5-carboxamide;

N-{(2*S*)-3-[4-(3-Chloro-4-cyanophenoxy)piperidin-1-yl]-2-hydroxypropyl}-*N*-methyl-2-oxo-4-(trifluoromethyl)-2,3-dihydro-1,3-thiazole-5-carboxamide;

N-{(2*R*)-3-[4-(2,4-Dichloro-3-methylphenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-oxo-4-(trifluoromethyl)-2,3-dihydro-1,3-thiazole-5-carboxamide;

N-{(2*R*)-3-[4-(3-Chloro-4-cyanophenoxy)piperidin-1-yl]-2-hydroxypropyl}-5-isopropyl-1*H*-1,2,3-triazole-4-carboxamide;

N-{(2*S*)-3-[4-(3-Chloro-4-cyanophenoxy)piperidin-1-yl]-2-hydroxypropyl}-5-isopropyl-*N*-methyl-1*H*-1,2,3-triazole-4-carboxamide;

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-oxo-4-(2,2,2-trifluoroethyl)-2,3-dihydro-1,3-thiazole-5-carboxamide;

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-oxo-4-pyridin-2-yl-2,3-dihydro-1,3-thiazole-5-carboxamide;

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-6-oxo-2-(pentafluoroethyl)-1,6-dihydropyridine-3–carboxamide;

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-5-(methylthio)-1*H*-1,2,3-triazole-4-carboxamide;

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-oxo-4-(trifluoromethyl)-2,3-dihydro-1,3-oxazole-5-carboxamide;

N-{(2*R*)-3-[4-(3 ,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-5-(trifluoromethyl)-1*H*-1,2,3-triazole-4-carboxamide;

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-5-[methyl(methylsulfonyl)amino]-1*H*-1,2,3-triazole-4-carboxamide;

N-{(2*R*)-3-[4-(3-Chloro-4-cyano-2-methylphenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-oxo-4-(trifluoromethyl)-2,3-dihydro-1,3-thiazole-5-carboxamide;

N-{(2*R*)-3-[4-(3-Chloro-4-cyanophenoxy)piperidin-1-yl]-2-hydroxypropyl}-5-(trifluoromethyl)-1*H*-1,2,3-triazole-4-carboxamide;

2-Chloro-5-[({(2*R*)-3-[4-(3,4-dichloro-2-methylphenoxy)piperidin-1-yl]-2-hydroxypropyl}amino)carbonyl]benzoic acid;

4-Chloro-3-[({(2*R*)-3-[4-(3,4-dichloro-2-methylphenoxy)piperidin-1-yl]-2-hydroxypropyl}amino)carbonyl]benzoic acid;

4-Chloro-3-[2-({(2R)-3-[4-(3,4-dichloro-2-methylphenoxy)piperidin-1-yl]-2-hydroxypropyl}amino)-2-oxoethoxy]benzoic acid;

{2-Chloro-5-[({(2R)-3-[4-(3,4-dichloro-2-methylphenoxy)piperidin-1-yl]-2-hydroxypropyl}amino)carbonyl]phenoxy}acetic acid;

3-[2-({(2*R*)-3-[4-(3,4-Dichloro-2-methylphenoxy)piperidin-1-yl]-2-hydroxypropyl}amino)-2-oxoethoxy]benzoic acid; or,

{3-[({(2R)-3-[4-(3,4-Dichloro-2-methylphenoxy)piperidin-1-yl]-2-hydroxypropyl}amino)carbonyl]phenoxy}acetic acid;

or a pharmaceutically aceptable salt thereof.

In a further aspect the invention provides the use of *N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2,3-dihydro-2-oxo-4-(trifluoromethyl)-5-thiazolecarboxamide, or a pharmaceutically acceptable salt thereof (for example a benzenesulfonate salt), in the manufacture of a medicament for the treatment of osteoarthritis or osteoarthrosis.

The invention also provides the benzenesulfonate salt of *N*-{3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2,3-dihydro-2-oxo-4-(trifluoromethyl)-5-thiazolecarboxamide (for example its (2*R*) enantiomer) for use in therapy or prophylaxis.

The invention further provides the use of the benzenesulfonate salt of *N*-{3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2,3-dihydro-2-oxo-4-(trifluoromethyl)-5-thiazolecarboxamide (for example its (2*R*) enantiomer), in the manufacture of a medicament for use in the treatment of a CCR3 mediated disease state (such as:

(1) (the respiratory tract) obstructive diseases of airways including: chronic obstructive pulmonary disease (COPD) (such as irreversible COPD); asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)}; bronchitis {such as eosinophilic bronchitis}; acute, allergic, atrophic rhinitis or chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis; sarcoidosis; farmer's lung and related diseases; nasal polyposis; fibroid lung, idiopathic interstitial pneumonia, antitussive activity, treatment of chronic cough associated with inflammatory conditions of the airways or iatrogenic induced cough;

(2) (bone and joints) rheumatic, infectious or autoimmune arthrides; seronegative spondyloarthropathies (such as ankylosing spondylitis, psoriatic arthritis or Reiter's disease); Behçet's disease; Sjogren's syndrome; or systemic sclerosis; or,

(3) (skin and eyes) psoriasis, atopic dermatitis, contact dermatitis or other eczmatous dermitides, seborrhoetic dermatitis, Lichen planus, Phemphigus, bullous Phemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitides erythemas, cutaneous eosinophilias, uveitis, Alopecia areata or vernal conjunctivitis;

in a warm blooded animal, such as man).

In another aspect the present invention provides a method of treating a CCR3 mediated disease state which comprises administering to a patient a therapeutically effective amount of the benzenesulfonate salt of *N*-{3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2,3-dihydro-2-oxo-4-(trifluoromethyl)-5-thiazolecarboxamide (for example its (2*R*) enantiomer).

In a further aspect the benzenesulfonate salt of *N*-{3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2,3-dihydro-2-oxo-4-(trifluoromethyl)-5-thiazolecarboxamide (for example its (2*R*) enantiomer) is useful in the treatment of asthma {such as bronchial,

allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)}; or rhinitis {including acute, allergic, atrophic or chronic rhinitis, such as rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis}.

In a still further aspect the benzenesulfonate salt of *N*-{3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2,3-dihydro-2-oxo-4-(trifluoromethyl)-5-thiazolecarboxamide (for example its (2*R*) enantiomer) is useful in the treatment of asthma.

The present invention also provides the use of the benzenesulfonate salt of *N*-{3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2,3-dihydro-2-oxo-4-(trifluoromethyl)-5-thiazolecarboxamide (for example its (2*R*) enantiomer) in the manufacture of a medicament for use in the treatment of asthma or rhinitis.

Compounds of formula (I) and their pharmaceutically acceptable salts have activity as modulators of chemokine receptor (for example CCR3) activity and are also H1 antagonists, and may be used in the treatment of arthritides associated with osteoarthritis or osteoarthrosis, both primary and secondary to, for example, congenital hip dysplasia.

According to a further feature of the invention there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in a method of treatment of osteoarthritis or osteoarthrosis of a warm blooded animal (such as man).

In another aspect of the present invention there is provided a method for treating osteoaerthritis or osteoarthrosis, in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of the formula (I), or a pharmaceutically acceptable salt thereof.

In order to use a compound of formula (I), or a pharmaceutically acceptable salt thereof, (active ingredient) for the therapeutic treatment of a warm blooded animal, such as man, said ingredient is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

The present invention also provides a composition comprising the benzenesulfonate salt of *N*-{3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2,3-dihydro-2-oxo-4-

(trifluoromethyl)-5-thiazolecarboxamide (for example its (2*R*) enantiomer) in admixture with a carrier, diluent or adjuvant.

Depending on the mode of administration, the pharmaceutical composition will, for example, comprise from 0.05 to 99%w (per cent by weight), such as from 0.05 to 80%w, for example from 0.10 to 70%w, such as from 0.10 to 50%w, of active ingredient, all percentages by weight being based on total composition.

A pharmaceutical composition can be administered in a standard manner for the disease condition that it is desired to treat, for example by topical (such as to the lung and/or airways or to the skin), oral, rectal or parenteral administration (for example, intra-articular). For these purposes the compounds of formula (I) may be formulated by means known in the art into the form of, for example, aerosols, dry powder formulations, tablets, capsules, syrups, powders, granules, aqueous or oily solutions or suspensions, (lipid) emulsions, dispersible powders, suppositories, ointments, creams, drops and sterile injectable aqueous or oily solutions or suspensions.

A suitable pharmaceutical composition is one suitable for oral administration in unit dosage form, for example a tablet or capsule which contains between 0.1mg and 1g of active ingredient.

Alternatively, a pharmaceutical composition is one suitable for intravenous, subcutaneous or intramuscular injection. Alternatively, a pharmaceutical composition is one suitable for intra-articular administration.

Each patient may receive, for example, an intra-articular, intravenous, subcutaneous or intramuscular dose of 0.01 $mgkg^{-1}$ to 100 $mgkg^{-1}$ of the compound, for example in the range of 0.1 $mgkg^{-1}$ to 20 $mgkg^{-1}$ of this invention, the composition being administered 1 to 4 times per day. The intra-articular, intravenous, subcutaneous or intramuscular dose may be given by means of a bolus injection. Alternatively, the intra-articular or intravenous dose may be given by continuous infusion over a period of time. Alternatively each patient can receive a daily oral dose which is approximately equivalent to the daily parenteral dose, the composition being administered 1 to 4 times per day.

The invention further relates to combination therapies or compositions wherein a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically

acceptable salt thereof, is administered concurrently (possibly in the same composition) or sequentially with an agent for the treatment of osteoarthritis or osteoarthrosis.

In particular a compound of formula (I) can be combined with a histamine type 1 receptor antagonist such as cetirizine, loratadine, desloratadine, fexofenadine, astemizole, acrivistine, terfenadine, promethazine, cyclizine, mizolastine, azelastine or chlorpheniramine; applied orally, topically or parenterally (for example intra-articularly).

The invention will now be illustrated by the following non-limiting Examples, in which, unless otherwise stated, the following abbreviations are used:-

DMEM is tissue culture medium Dulbecco's Modified Eagles Medium

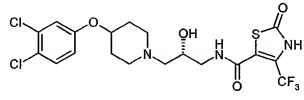
PSG is a combination of penicillin, streptomycin and L-glutamine

FCS is foetal calf serum

NEAA is Non essential amino acids

Example 1

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2,3-dihydro-2-oxo-4-(trifluoromethyl)-5-thiazolecarboxamide benzenesulfonate



Step 1: *N*-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2,3-dihydro-2-oxo-4-(trifluoromethyl)-5-thiazolecarboxamide

A solution of ethyl 2,3-dihydro-2-oxo-4-(trifluoromethyl)-5-thiazolecarboxylic acid (85.252 g) was dissolved in thionyl chloride (500 mL) and heated at reflux overnight. The solution was cooled to room temperature, concentrated *in vacuo*, and residual thionyl chloride was azeotroped with toluene (2 x 100 mL). The residue was dissolved in dry tetrahydrofuran (250 mL) and the resulting solution was added dropwise over 3 h to a suspension of (2*R*)-1-amino-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]propan-2-ol (127.7 g) and triethylamine (111.5 mL) in tetrahydrofuran (1250 mL). The yellow mixture was stirred at room temperature overnight and the solution was concentrated *in vacuo* to leave a yellow gum (313 g). This was dissolved in water (pH 7-8) and acidified to pH 1-2 with dilute hydrochloric acid. The solid was extracted with ethyl acetate (2 L + 500 mL), and

sodium chloride added to the aqueous layer to salt out the remaining organics. The combined organic extractions were dried (Na_2SO_4), concentrated *in vacuo* and vacuum dried for 42 hours to leave a yellow foam (217 g).

MS (APCI-ve) 512/514 $[M-H]^-$

^1H NMR δ (CD_3OD) 2.00 – 2.40 (4H, m), 3.19 (2H, m), 3.40 (2H, m), 3.20 – 3.60 (4H, m), 4.16 – 4.24 (1H, m), 4.65 - 4.85 (1H, m), 6.98 (1H, dd), 7.23 (1H, s), 7.43 (1H, d).

Step 2: *N*-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2,3-dihydro-2-oxo-4-(trifluoromethyl)-5-thiazolecarboxamide benzenesulfonate

The yellow foam from Step 1 (above) was dissolved in methanol (400 mL) and treated with benzenesulfonic acid (63.27 g), stirred at room temperature for 2 hours, filtered and concentrated *in vacuo* to leave a yellow foam (297 g). This was dissolved in hot ethyl acetate (about 800 mL) and allowed to cool to room temperature. The resulting suspension was stirred at room temperature for 72 hours, filtered, washed with ethyl acetate (500 mL), air dried, and vacuum dried in an oven at 40 °C to leave a white powder (177.5 g).

Elemental analysis: C: 44.32%(44.65); H: 3.86%(3.90); N: 6.38%(6.25);
S: 9.66%(9.53)

MS (APCI-ve) 512/514 $[M-H]^-$

^1H NMR δ (d_6-DMSO) 1.88 - 2.26 (4H, m), 3.11 (2H, m), 3.24 – 3.32 (2H, m), 2.86 - 3.46 (4H, m), 4.02 – 4.10 (1H, m), 4.64 – 4.72 (1H, m), 7.02 (1H, dd), 7.24 – 7.30 (4H, m), 7.50 (1H, d), 7.60 – 7.64 (2H, m), 8.37 (1H, s).

Example 2

Characterisation of the activity of *N*-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-6-oxo-2-(pentafluoroethyl)-1,6-dihydropyridine-3–carboxamide (Example 35 in WO 2005/073192)

Methods

(i) Isolation of human articular chondrocytes (HAC) from OA cartilage for histamine stimulation.

HAC are isolated from cartilage from osteoarthritic tissues removed at joint replacement. Cartilage is incubated overnight in 2mg/ml collagenase in DMEM + 10% FCS +PSG at 37°C, with shaking. The resulting cell suspension is filtered to remove undigested cartilage and the cells are centrifuged at 1200 rpm for 10 minutes. Cells are resuspended in DMEM plus 10% FCS PSG/NEAA/fungizone/gentamycin, plated at approx $5x10^{-6}$ in a T-75 and grown to confluence. Cells are subsequently plated at approx 10,000 cells per well into 96 well plates for stimulation with histamine. Triplicate wells of first passage HAC are treated with either DMEM (10% or 0% FCS) alone (control), or DMEM (10% or 0% FCS) plus histamine (dose range 10nM up to 1mM). Cells are incubated at 37°C for 24 hours, the conditioned medium harvested, and assayed for PGE2, MMP or cytokine production by enzyme linked immunosorbent assay (ELISA). In addition, cells are harvested for RNA analysis, in Qiagen RLT buffer containing 1% β-mercaptoethanol.
For some experiments cells are incubated with specific antagonists for 20 minutes prior to, and in combination with, histamine stimulation.

(ii) Chemokine stimulation of human cartilage explant

Explant preparation

Human osteoarthritic cartilage is obtained during total knee replacement surgery. Full-depth cartilage slices are obtained from both the femoral condyles and the tibial plateau and explant discs removed using a 5 mm diameter KAI sterile dermal biopsy punch. After dissection, the explants are all pooled in a Petri dish. For each condition, sixteen explants are randomly taken from the Petri dish and cultured in polypropylene 96-well plates with phenol red free Dulbecco's Modified Eagle Medium (DMEM; Gibco, Grand Island, NY), 150 μg/ml gentamicin, 1.5 μg/ml fungizone and 100 units/ml penicillin, 100 μg/ml streptomycin and L-Glutamine.

After an initial 48 hour pre-stimulation, rest period, experimental reagents are added for 24, 48 or 96 hours. Explants are incubated with the appropriate concentration of compound alone, or DMSO as a control, for 20 minutes prior to addition of the chemokine. Cartilage is subsequently treated with either vehicle control (plus DMSO); chemokine (at 30-

300ng/ml) plus DMSO; or chemokine (30ng/ml) plus the compound of Example 1. Conditioned media are collected 24, 48 or 96 hours post stimulation and stored at -20°C prior to analysis. Cartilage explants are also collected and snap frozen in liquid nitrogen, prior to RNA extraction.

Extraction of RNA from cartilage explants

Each condition is composed of sixteen cartilage explant discs, which are pooled prior to snap freezing in liquid nitrogen. These pooled samples are ground to a fine powder under liquid nitrogen then resuspended in 10ml trizol in polypropylene Oakridge tubes, and RNA extracted according to the manufacturer's protocol. The RNA pellet is resuspended in approx 500µl RNAse and DNAse free water and then combined with 1.75ml Qiagen RLT. RNA is further purified with Qiagen RNEasy mini columns (Qiagen Cat# 74104), as decribed in the manufacturer's protocol, including on column DNA digestion. The RNA obtained by these procedures is analysed using Agilent bioanalyser technology, according to the manufacturer's instructions, to determine the quantity and quality.

Gene Expression analysis: the 96 and 48 gene fingerprints using low density arrays (Q-PCR)

Low-density gene arrays [quantitative polymerise chain reaction (Q-PCR) method] with either 96 or 48 genes pertinent to OA (as identified by Affymetrix microarray analysis of OA articular cartilage) are used to assess the effects of treating human diseased cartilage explants with the chemokines eotaxin-2 or RANTES, alone or in combination with the compound of Example 1. Gene expression changes were reported as fold change normalised against a standard non-affected gene: GAPDH.

(iii) *In vivo* functional validation of histamine-induced responses murine articular knee joint

It is hypothesised that histamine released by trafficking mast cells or by the de novo synthesis of histamine by articular chondrocytes induces a H1-dependant increase in COX-

2 mRNA expression and elevated PGE2 synthesis in synovial fibroblasts and articular chondrocytes. To evaluate the role of histamine in pathological processes in the joint, a pharmacodynamic mouse model was developed to investigate the effect of intra-articular injection (IAI) of histamine on joint swelling using calliper measurements, and measuring PGE2 and /or Il-6 levels from synovial knee joint lavages.

Adult C57Bl6 mice were dosed with either vehicle or test compound 1 hour prior to intra-articular injection of histamine (5μmol). Swelling was induced by injection of 6μl of histamine/saline suspension into the knee joint cavity under inhalation anaesthesia with isoflurane. Joint swelling was quantified by calliper measurements taken at 1, 6, 12, 24, 36 and 48hr. Terminal synovial fluid knee lavages were sampled and levels of the inflammatory mediator Il-6 were measured in the fluid from synovial knee joint lavages.

Results

Histamine Induced Joint Oedema

In the murine articular knee joint studies, Intra-articular injection of histamine gave a 5-fold increase in joint oedema compared to vehicle control animals. This swelling was almost completely ablated with desloratadine treatment (5.1 mg/kg).

Histamine induced IL-6 in joint lavage

Elevated IL-6 levels have been have been observed in a number of pathological conditions, including inflammation. Induction of joint swelling by histamine injection resulted in > 60% increase in release of IL-6 into the synovial fluid. All doses of desloratadine significantly inhibited IL-6 release comparable to basal levels measured for control samples (Figure 1).

Taken together, these results show that amelioration of histamine-induced joint swelling is correlated with a reduction in synovial fluid IL-6 protein to near basal level. On this basis, the ability to limit IL-6 expression in this way can be taken to be indicative of a compound's potential activity in controlling joint swelling.

(iii) *In vitro* functional validation of histamine-induced responses in isolated human articular chondrocytes

It has previously been reported that histamine induces an increase in PGE2 release by primary chondrocytes (Tetlow & Woolley 2004). In our studies we observed a histamine induced, dose dependent increase in release of PGE2 (n=6) (Figure 2), and an increase in Cox2 mRNA expression levels in isolated human chondrocytes. These responses to histamine were inhibited by the H1R selective antagonists desloratidine (10nM) and cetirizine (100nM) (Figure 2), showing that Histamine stimulated release of the pain mediator, PGE2, from isolated human chondrocytes can be abrogated by H1R antagonists.

In vitro functional validation of CCR3 mediated responses in human articular chondrocytes/cartilage

CCR3 ligands have been implicated in the pathogenesis of osteoarthritis due to their ability to modulate cartilage integrity, by increasing MMPs and stimulating loss of proteoglycans (Alaaedine et al 2001; Hsu et al 2004). The functional role of CCR3 in human cartilage explant culture by analysing the gene expression changes seen in this system in response to stimulation with ligands for CCR3 was investigated. In response to Eotaxin 2 stimulation of human explant cartilage (donor KM 014_04) an increased expression of the pro-inflammatory cytokines IL-6 (14 fold) and IL-8 (11 fold) was observed. Importantly, CCR3 ligands up-regulated the metalloproteinases MMP1 (8.8 fold), MMP2 (4 fold) and MMP13 (x 3.5 fold) with no concommitant change in expression of the endogenous MMP inhibitors, TIMP 1, 2 or 3. Enhanced expression of the aggrecanases, ADAMTS4 (3.6 fold) and ADAMTS 5 (6 fold) was also observed. Finally, periostin a protein postulated to be involved in the process of matrix mineralisation in OA, was modestly elevated (2 fold). These changes in gene expression were confirmed by Q-PCR analysis and ELISA. Expression of ADAMTS4, MMP13, IL-6, IL-8 and MMP2 mRNA was examined in explant cartilage from a range of donors, and a greater than 2 fold increase in mRNA expression in response to CCR3 ligands was observed in the majority of OA donors and could be inhibited by the compound of Example 1 at 3x pA2, n=3 (Figure 3). {The y-axis of the right-hand graph in Figure 3 (the graph headed IL6) represents the Ratio IL6/GAPDH.}

Example 3

A phase II, randomised, double blind, placebo controlled, parallel-group, multi-centre exploratory study to investigate the effect on clinical markers, biomarkers of collagen turnover, safety and tolerability of a compound of formula (I), or a pharmaceutically acceptable salt thereof, given orally in tablet form once daily for 4 weeks, in patients with osteoarthritis of the knee.

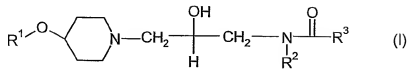
The objectives of the study are to evaluate the clinical effect of the compound of formula (I), or a pharmaceutically acceptable salt thereof, compared with placebo by assessing the change from baseline in WOMAC™ subscales (pain, stiffness and physical function), and the physician and patient global disease assessment. The primary collagen turnover biomarkers are planned to be CTX-II, PIIANP and uGGP (Glc-Gal-PYD).

The compound of formula (I) is, for example, the benzenesulfonate salt of *N*-{3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2,3-dihydro-2-oxo-4-(trifluoromethyl)-5-thiazolecarboxamide (for example its (2*R*) enantiomer).

- WOMAC™ index (WOMAC™ 3.1 index) is an official scoring system using a battery of 24 questions. For more information see www.womac.org/womac/index.htm.
- CTX-II is a type-II collagen neo-epitope generated by MMP cleavage of type-II collagen. It is a marker of cartilage degradation.
- PIIANP is the type II collagen pro-collagen alpha chain. It is a marker of cartilage synthesis.
- uGGP is a maturation product of 2 hydroxyl-lysine residues from collagen C or N telopeptides with glycosylated hydroxylysine from the alpha-helix of collagen. It is a marker of synovial inflammation.
- Tablet form comprises compound of formula (I), or a pharmaceutically acceptable salt thereof, microcrystalline cellulose, mannitol, sodium starch glycolate, hydroxypropylcellulose and sodium stearyl fumarate.

CLAIMS

1. Use of a compound of formula (I)



(I)

wherein:

R^1 is phenyl optionally substituted by halogen, cyano, C_{1-4} alkyl or C_{1-4} haloalkyl;

R^2 is hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl; and

R^3 is a group having an NH or OH that has a calculated or measured pKa of 1.0 to 8.0; or a pharmaceutically acceptable salt;

in the manufacture of a medicament for the treatment of osteoarthiritis or osteoarthrosis.

2. Use according to claim 1 wherein R^1 is phenyl substituted with one, two or three of: halogen, cyano or C_{1-4} alkyl

3. Use according to claim 1 or claim 2 wherein R^2 is hydrogen.

4. Use according to any preceding claim wherein the acidic NH of R^3 is part of a ring or is part of a substituent on an aryl or heterocyclyl ring.

5. Use according to any preceding claim wherein R^3 is:

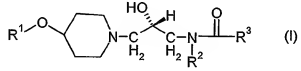
- 2-oxo-thiazol-5-yl having a suitable electron withdrawing substituent in the 4-position;
- 2-oxo-oxazol-5-yl having a suitable electron withdrawing substituent in the 4-position;
- 1H-1,2,3-triazol-4-yl having a suitable substituent in the 5-position;
- 4-oxo-1H-1,4-dihydropyridin-3-yl having a suitable electron withdrawing substituent in the 2-position;
- 2,6-dioxo-1H-1,2,3,6-tetrahydropyrimidin-4-yl having a suitable substituent in

the 3-position and optionally substituted in one or more other ring positions;

- 6-oxo-1H-1,6-dihydropyridin-3-yl having a suitable electron withdrawing substituent in the 2-position and/or the 5-position and optionally substituted in one or more other ring positions;
- 6-oxo-1H-1,6-dihydropyridin-3-yl having CH_2CO_2H on the ring nitrogen and optionally substituted in one or more other ring positions;
- 2H-tetrazol-5-yl;
- a CO_2H, CH_2CO_2H or OCH_2CO_2H group on an optionally substituted phenyl, optionally substituted CH_2Ophenyl, optionally substituted naphthyl ring; or,
- an $NHS(O)_2(C_{1-4}$ alkyl) group on an optionally substituted aromatic heterocyclyl ring;

or, where possible, a tautomer thereof.

6. Use according to any preceding claim wherein the 2-hydroxy group has the stereochemistry:



(I)

7. Use of a compound of formula (I) as defined in any preceding claim in combination with a histamine type 1 receptor antagonist in the manufacture of a medicament for the treatment of osteoarthiritis or osteoarthrosis.

8. A method for treating osteoarthritis or osteoarthrosis in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of the formula (I) as defined in claim 1, or a pharmaceutically acceptable salt thereof.

9. A method according to claim 8 comprising administering an effective amount of a compound of formula (I) in combination with an effective amount of a histamine type 1 receptor antagonist.

10. The benzenesulfonate salt of *N*-{3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2,3-dihydro-2-oxo-4-(trifluoromethyl)-5-thiazolecarboxamide.

11. The benzenesulfonate salt of *N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2,3-dihydro-2-oxo-4-(trifluoromethyl)-5-thiazolecarboxamide.

12. A process for the preparation of a compound claimed in claim 10 or 11, the process comprising treating *N*-{3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2,3-dihydro-2-oxo-4-(trifluoromethyl)-5-thiazolecarboxamide, in racemic form or in as the (2*R*) enantiomer, with benzenesulfonic acid in a suitable solvent at ambient temperature.

13. A composition comprising a compound as claimed in claim 10 or 11 in admixture with a carrier, diluent or adjuvant.

14. A compound claimed in claim 10 or 11 for use in therapy or prophylaxis.

15. The use of the compound claimed in claim 10 or 11 in the manufacture of a medicament for use in the treatment of a CCR3 mediated disease state.

16. A method of treating a CCR3 mediated disease state which comprises administering to a patient a therapeutically effective amount of a compound as claimed in claim 10 or 11.

Figure 1

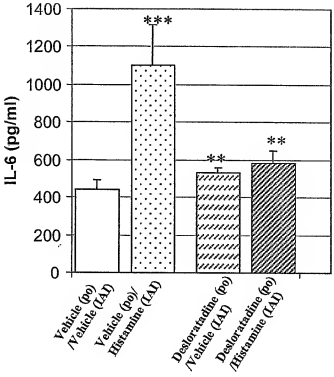

1400
1200
1000
800
600
400
200
0
IL-6 (pg/ml)
***
**
**
Vehicle (po) /Vehicle (IAI)
Vehicle (po)/ Histamine (IAI)
Desloratadine (po) /Vehicle (IAI)
Desloratadine (po) /Histamine (IAI)

Figure 2

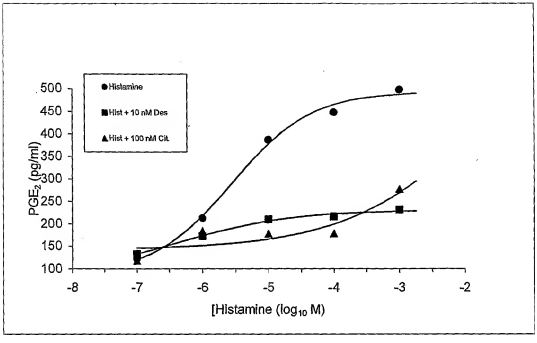
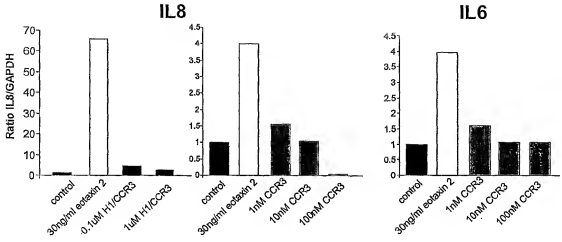

Histamine
Hist + 10 nM Des
Hist + 100 nM Cit
PGE2 (pg/ml)
500
450
400
350
300
250
200
150
100
-8
-7
-6
-5
-4
-3
-2
[Histamine (log10 M)

Figure 3


IL8
IL6
Ratio IL8/GAPDH
control
30ng/ml eotaxin 2
0.1uM H1/CCR3
1uM H1/CCR3
1nM CCR3
10nM CCR3
100nM CCR3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2007/000321

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 8-9, 16
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 8-9, 16 relate to a method of treatment of the human or animal body by surgery or by therapy, as well as diagnostic

.../...

2. ☒ Claims Nos.: 1-7
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Present claims 1-7 relate to a compound defined by reference to a desirable characteristic or property, namely pKa-value

.../...

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Box II.1

methods /Rule 39.1(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds.

Box II.2

(R3) and the expression "suitable electron withdrawing". The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and / or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. Additionally, previously known compounds may be included in the scope of the present claims. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds mentioned in the description on pages 11-14.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2007/000321

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: A61K, A61P, C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ, CHEMICAL ABSTRACTS DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005073192 A1 (ASTRAZENECA AB), 11 August 2005 (11.08.2005), page 13, line 18; page 28, example 4	1-7,10-15
A	WO 9639386 A1 (SCHERING CORPORATION), 12 December 1996 (12.12.1996)	

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 July 2007	05 -07- 2007
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anna Sjölund/CM Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (April 2007)

International patent classification (IPC)
A61K 31/4465 (2006.01)
A61K 31/454 (2006.01)
A61P 19/02 (2006.01)
C07D 417/12 (2006.01)

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- e-tjänster/anförda dokument (service in Swedish).

Use the application number as username.
The password is **YVOCCQNVIP**.

Paper copies can be ordered at a cost of 50 SEK per copy from PRV InterPat (telephone number 08-782 28 85).

Cited literature, if any, will be enclosed in paper form.

WO	2005073192	A1	11/08/2005	AR	049770	A 06/09/2006
				AU	2005207817	A 11/08/2005
				CA	2553089	A 11/08/2005
				CN	1938274	A 28/03/2007
				EP	1713772	A 25/10/2006
				KR	20060128992	A 14/12/2006
				NO	20063921	A 02/11/2006
				SE	0400208	D 00/00/0000
				US	20070054924	A 08/03/2007
WO	9639386	A1	12/12/1996	AT	207897	T 15/11/2001
				AU	706744	B 24/06/1999
				AU	5950996	A 24/12/1996
				CA	2198238	A 12/12/1996
				CN	1085661	B,C 29/05/2002
				CN	1161033	A 01/10/1997
				DE	69616480	D,T 11/07/2002
				EP	0773929	A,B 21/05/1997
				ES	2162061	T 16/12/2001
				HK	1008819	A 00/00/0000
				HU	9701281	A 28/11/1997
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				US	5654316	A 05/08/1997